Bipolar disorders

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Abstract | Bipolar disorders are chronic and recurrent disorders that affect >1% of the global population. Bipolar disorders are leading causes of disability in young people as they can lead to cognitive and functional impairment and increased mortality, particularly from suicide and cardiovascular disease. Psychiatric and nonpsychiatric medical comorbidities are common in patients and might also contribute to increased mortality. Bipolar disorders are some of the most heritable psychiatric disorders, although a model with gene–environment interactions is believed to best explain the aetiology. Early and accurate diagnosis is difficult in clinical practice as the onset of bipolar disorder is commonly characterized by nonspecific symptoms, mood lability or a depressive episode, which can be similar in presentation to unipolar depression. Moreover, patients and their families do not always understand the significance of their symptoms, especially with hypomanic or manic symptoms. As specific biomarkers for bipolar disorders are not yet available, careful clinical assessment remains the cornerstone of diagnosis. The detection of hypomanic symptoms and longtudinal clinical assessment are crucial to differentiate a bipolar disorder from other conditions. Optimal early treatment of patients with evidence-based medication (typically mood stabilizers and antipsychotics) and psychosocial strategies is necessary.

Bipolar disorders include several disorders of emotion, energy and thought that are characterized by biphasic mood episodes of mania or hypomania and depression and are expressed as recurrent episodes of changes in energy levels and behaviour. Cognitive symptoms, especially altered reaction time, verbal and visual memory and executive function, are highly prevalent in patients and contribute to disability[1].

Bipolar disorders have been traditionally classified either as part of the spectrum of psychoses (especially as part of the most severe end of the spectrum, which corresponds to the classic concept of manic–depressive psychosis) or as a mood disorder (an affective disorder), potentially as a continuum from unipolar depression to bipolar illness[2]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) created a category for 'Bipolar and Related Disorders'; thus, bipolar disorders are not classified under either psychotic disorders or affective disorders[3]. However, bipolar disorder is classified under the mood disorders block in the International Classification of Diseases, 10th revision (ICD-10)[4]. In the DSM-5, bipolar disorders are subclassified as bipolar I disorder, bipolar II disorder, cyclothymia and residual categories of atypical forms that do not fit in the abovementioned subtypes. This subclassification depends on the severity and duration of manic (or hypomanic) and depressive episodes (FIG. 1).

During manic episodes, hyperactivity, increased self-esteem, grandiosity, reduced need for sleep, expansive mood and behaviour and psychotic symptoms are common, whereas during depressive episodes, decreased energy, sadness, social withdrawal, hypersomnia and low self-esteem are the cardinal features. Psychosis can also occur during depressive episodes but occurs more frequently during mania. Hypomania is a milder and shorter form of mania, and individuals with hypomania have relatively intact judgement. Often, acute episodes of mood alterations can include symptoms at both poles (that is, mixed symptoms).

Patients with bipolar disorders might be able to achieve full remission and have symptom-free periods, during which the disorder is assumed to be latent, with optimal management. However, in many cases, residual and subthreshold symptoms persist in a pervasive way, making functional recovery difficult to achieve, especially after the second, third and subsequent episodes. Management involves pharmacological and nonpharmacological treatments for acute phases in manic (or hypomanic) and depressive episodes and long-term therapy to prevent episode recurrence.

In this Primer, we provide an overview of the current state of knowledge of bipolar disorders, including the epidemiology, pathophysiology, diagnosis, course of illness, treatment, prevention and psychosocial outcome of these disorders.

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Article number: 18008
doi:10.1038/nrdp.2018.8
Published online 8 Mar 2018

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Epidemiology

Bipolar disorders affect >1% of the global population[5]. The estimated lifetime prevalence is 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, 1.4% for subthreshold manifestations of bipolar disorders and 2.4% for the broader bipolar spectrum of bipolar disorders[5]. Some studies have suggested higher rates: for example, a global 12-month prevalence of 1.5% and a lifetime prevalence of 2.1% for bipolar I disorder according to DSM-5 criteria have been reported[6]. The onset of bipolar disorders is independent of ethnicity, nationality and socioeconomic status. The prevalence of bipolar I disorder is similar in men and women, but bipolar II disorder is more common in females[7].

Bipolar disorders begin in youth, with a mean age of onset of ~20 years[2]. An earlier age of onset has been associated with greater comorbidity and onset beginning with depression. Diagnosis and management usually commence in young adulthood[8]. However, a 5-year delay to diagnosis from the onset of symptoms has been shown in some studies, although variable data have been reported[8]. In addition, time to diagnosis is longer in patients with comorbidities and depressive onset polarity[8]. Importantly, the duration of untreated illness (that is, the time between the first episode and adequate management) drives prognosis, and a longer duration of untreated illness has been associated with an increased number of suicide attempts and a longer duration of illness[9].

Estimates of the global burden of disease have shown that 5 of the top 20 causes of disability are due to mental illnesses[10]. Bipolar disorders are the 17th leading cause of global burden of disease, after depression, anxiety disorders, schizophrenia and dysthymia[10]. Mental illness accounted for 32.4% of years lived with disability and 13.0% of disability-adjusted life years out of all disorders included in the Global Burden of Disease Study[10]. Indeed, as a lifelong and recurrent illness, bipolar disorders often lead to functional impairment and reduced quality of life (see Quality of life)[11]. This burden extends to family members, with caregiver burden and depression being common[12]. In addition, as bipolar disorders affect the economically active population, high costs to society are incurred in terms of direct health-care costs and the costs of disability, of which the costs of disability predominate[13]. This impact is likely greatest in younger individuals, as bipolar disorders disrupt the attainment of age-specific developmental, relationship, educational and occupational milestones[14].

Comorbidities

Bipolar disorders are comorbid with other psychiatric disorders (including anxiety disorders, substance use disorders, attention-deficit/hyperactivity disorder and personality disorders), which can make diagnosis and management of bipolar disorders more difficult; this comorbidity is also associated with poorer outcomes[15]. Nonpsychiatric comorbidities are similarly highly prevalent in patients with bipolar disorders and include metabolic syndrome, diabetes mellitus, osteoporosis and fibromyalgia as well as other endocrine and cardiovascular disorders[16–18]. Regarding metabolic syndrome, the principal drivers include an unhealthy lifestyle and use of antipsychotic medications rather than illness itself[19]. The presence of comorbid disorders has been associated with a greater risk of premature mortality in patients with bipolar disorders than in the general population[20]. In addition, comorbid obesity is associated with poorer outcomes of bipolar disorders with lithium-based or quetiapine-based treatment[21]. A later-in-life onset of mania might be suggestive of an underlying medical comorbidity[22].

Suicide

Among the affective disorders, bipolar disorders have the highest suicide rate[23], which is up to 20-times higher than the rate among the general population. Approximately one-third to one-half of patients with bipolar disorders will attempt suicide at least once, and ~15–20% of suicide attempts are lethal[24]. Risk factors for suicide attempts include a younger age at onset, female sex, depressive polarity, anxiety, substance abuse and personality disorder comorbidity; risk factors for completed suicide include a first-degree family history of suicide and male sex[24]. The risk of suicide is higher in untreated patients than those treated with antiepileptic drugs[25].

Mechanisms/pathophysiology

Genetics

Bipolar disorders are genetically complex disorders with a multifactorial genesis: both genetic factors, such as common and rare variants, and environmental factors contribute[26,27]. The heritability of bipolar disorders is estimated to be up to 85%[2], which is one of the highest

estimates for psychiatric disorders, although a multifactorial model of gene–environment interaction is believed to best fit this disorder (FIG. 2). Although early association studies focused on candidate genes, genome-wide association studies (GWAS) have evaluated large numbers of common variants (single-nucleotide polymorphisms) across the whole genome for associations with disease. These GWAS have produced long-awaited robust and reproducible findings. Thus far, significant genetic associations have been detected in 18 regions throughout the genome, many of which have been replicated (TABLE 1). As the associated alleles have small effects (with ORs <1.3), very large case–control samples are needed to validate these findings. As sample sizes continue to increase, in particular through the formation of large international consortia (such as the Consortium on Lithium Genetics), more robust findings are expected. First pathway analyses have suggested major roles for calcium signal transmission, the glutamatergic system, hormone regulation, microRNAs and histone and immune pathways, although these data are preliminary[28,29]. Interestingly, intracellular calcium signalling was suggested to have a role in the pathophysiology of bipolar disorders several decades ago[30].

In addition to the common variants detected in GWAS, rare variants can also be relevant for disease development if they have a high penetrance and, therefore, convey an increased risk of the disease. Rare variants are classified according to their genomic size into single-nucleotide variants, smaller insertions and deletions and larger copy number variants (CNVs; deletions or duplications of large DNA sequences of 1 kb to 3 Mb that often affect several genes). Thus far, the most extensive results are available for CNV studies, but compared with other neuropsychiatric conditions such as schizophrenia, autism spectrum disorder and intellectual disability, these studies in bipolar disorders have not produced robust results. Some studies showed the accumulation of rare CNVs in patients with bipolar disorders, especially in those with early-onset disease[31,32]; however, these findings could not always be reproduced. One meta-analysis reported an association between three CNVs and bipolar disorders (duplications at 1q21.1 and 16p11.2 and deletions at 3q29 (REF. 33)) that had all previously been associated with schizophrenia. In addition to GWAS and CNV studies, next-generation sequencing approaches to bipolar disorders are expected to discover novel rare variants and corroborate previous findings.

Two decades of intense genetic research into bipolar disorders have focused on improving our understanding of the aetiology and how the disorders overlap with other mental disorders such as schizophrenia or major depressive disorder[34]. At present, genetic variants that have been associated with bipolar disorders cannot be used to predict individual risk, the course of the disorders or the effects of medication. Furthermore, the polygenic nature of these disorders makes it unlikely that a deterministic prediction will be possible in the future[35]. Taking into account ongoing studies, we speculate that ~100 loci will be identified from GWAS for bipolar disorders and major depressive disorder combined, which will narrow the gap between these conditions and schizophrenia, for which >100 loci have been identified. The GWAS are complemented by CNV studies and next-generation sequencing approaches and, collectively, data from these studies should improve our understanding of the pathways and mechanisms underlying bipolar disorders and related traits. In addition, these data could potentially spur the development of novel pharmacological targets or lead to innovative drug repurposing trials.

Although most genetic studies of bipolar disorders have focused on aetiology, another area of research — pharmacogenetics — has been attracting increasing attention. Pharmacogenetics is the influence of genetic variation on the pharmacokinetics and pharmacodynamics of pharmacological therapies and could, in principle, contribute to personalized medicine. Pharmacogenetics studies in bipolar disorders have mainly encompassed candidate gene studies with small samples and have focused on lithium response. Because of the small sample sizes of these studies and the different phenotypic definitions applied, no robustly replicated findings have been produced[36]. The largest GWAS for lithium response included 2,563 patients from >20 clinical centres in 4 continents, was performed by the Consortium on Lithium Genetics and reported a significant association with a locus on chromosome 21, which encodes the long, non-coding RNAs AL157359.3 and AL157359.4 (REF. 37). In addition, a poorer response to lithium in patients with bipolar disorders who have

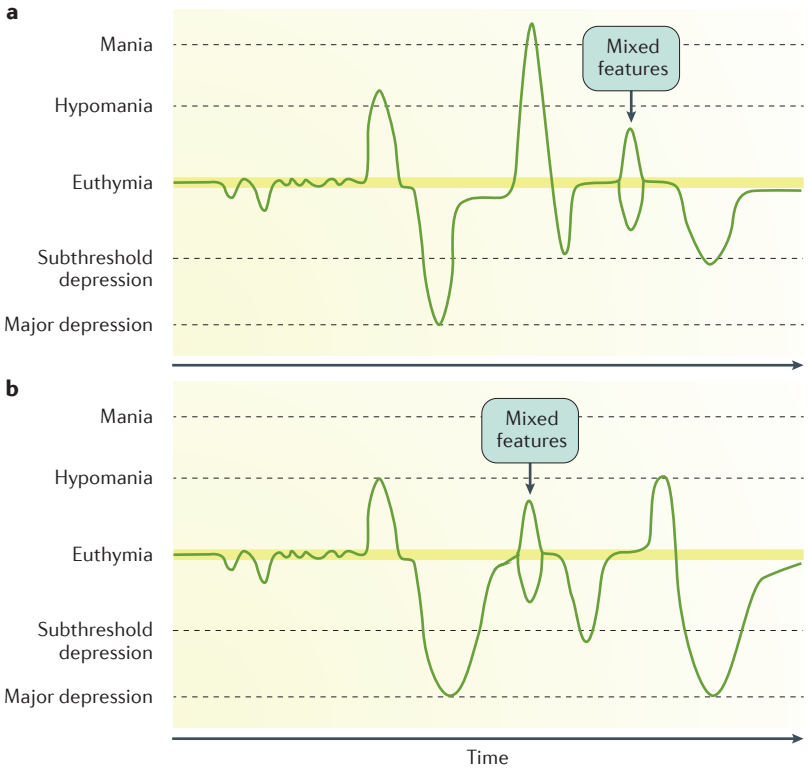

Figure 1 | **Main subtypes of bipolar disorder.** Bipolar I disorder is characterized by at least one episode of mania (part **a**), whereas bipolar II disorder is characterized by at least one hypomanic and one depressive episode (part **b**). Mixed features can occur in both disorders.

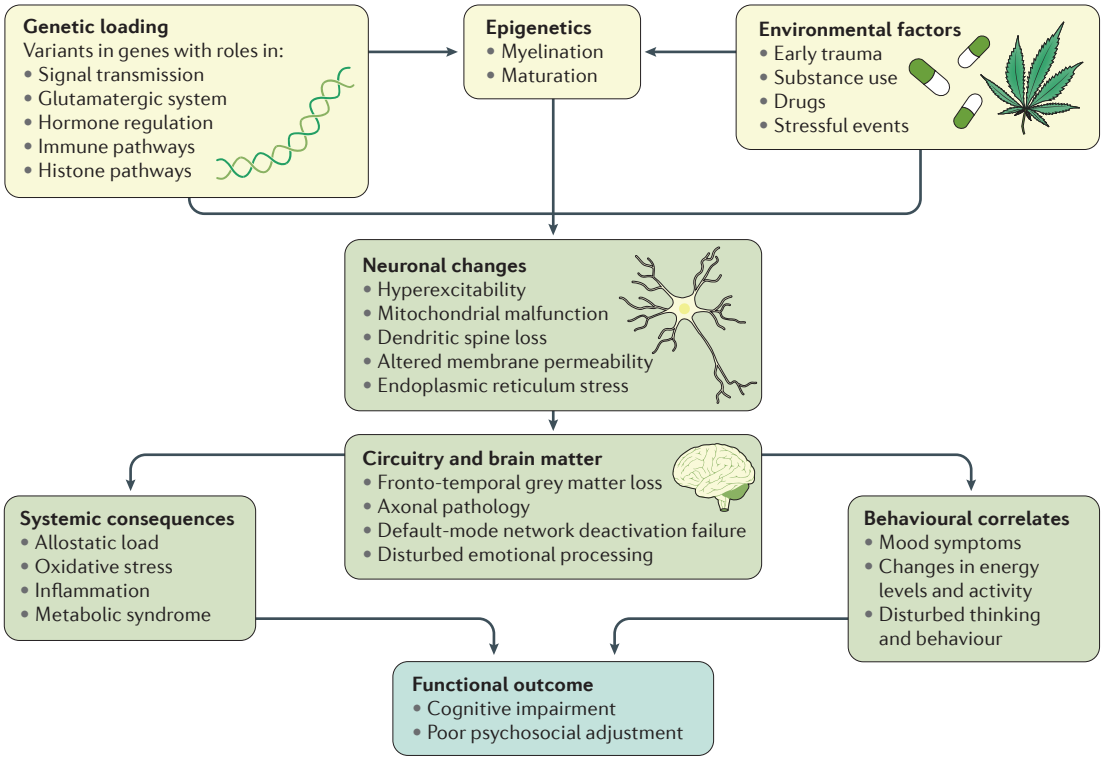

Figure 2 | **Multifactorial model of bipolar disorders.** Although bipolar disorders are amongst the most heritable psychiatric disorders, both genetic and environmental factors contribute to disease development. Gene–environment interactions might be mediated by epigenetic alterations. Genetic and environmental factors might contribute to the development of bipolar disorders through neuronal changes that modify brain circuitry. These changes systemically and behaviourally affect the body, leading to psychosocial and cognitive impairment.

a higher genetic loading for schizophrenia has been reported by the Consortium on Lithium Genetics[38]. Despite these data, research on pharmacogenetics is still in its infancy; further replication studies are necessary and causal associations between the associated markers and their expression need to be evaluated.

Environmental and medical risk factors

Although bipolar disorders have high heritability, environmental factors that can modify the onset and course of the disorders should also be taken into account. In general, the literature on the role of environmental factors in bipolar disorders is limited, although several environmental factors have been identified. For example, perinatal risk factors such as caesarean section delivery[39], maternal influenza infection[40], maternal smoking during pregnancy[41] and high paternal age[42] have been implicated in increasing the risk of bipolar disorders. Life events, particularly childhood adverse events, have classically been described as risk factors of bipolar disorders as well as predictors of a more-torpid course[43,44]. Drug misuse has the same role. Indeed, the consumption of cannabis or other drugs during adolescence might lead to the early onset of bipolar disorders and a more-severe course[45]. In addition, as most patients with bipolar disorders present with a depressive episode, they receive treatment with antidepressants without mood stabilizers, which can induce hypomanic or manic episodes[46]. Thus, the use of antidepressants might 'unmask' bipolar disorders. Other therapies that have been associated with mood switches in bipolar disorders are corticosteroids, androgens, electroconvulsive therapy (ECT), isoniazid and chloroquine[2]. Medical conditions that have been associated with risk of bipolar disorders are multiple sclerosis, stroke, systemic lupus erythematosus and endocrine disorders (such as Cushing syndrome and Addison disease)[2]. Indeed, subthreshold hypothyroidism has been closely associated with rapid-cycling bipolar disorders[47]. In addition, change of season, in particular from winter to spring and from summer to autumn[48], and increased light exposure[49] have also been described as triggers of bipolar disorders as well as course predictors.

Pathophysiology

Knowledge of the pathogenesis and pathophysiology of bipolar disorders has progressed rapidly with advances in molecular technologies. Historically, mood disorders were though to result from an imbalance in the monoamine neurotransmitter systems, including the serotonergic, noradrenergic and — in particular — dopaminergic pathways[2]. However, no singular dysfunction in these systems has been identified[2]. Altered endocrine functions have been widely studied in mood disorders, including the analysis of hormone levels in the blood and urine and the evaluation of the

neuroendocrine systems, particularly the hypothalamic–pituitary–thyroid axis and the hypothalamic–pituitary–adrenal axis[2] (FIG. 2). The early rebound of cortisol in the dexamethasone suppression test has been generally reported in affective illness[50].

Current studies are more focused on the modulation of synaptic and neural plasticity in brain regions, such as the prefrontal cortex, hippocampus, amygdala and other regions of the limbic system, in bipolar disorder[51,52] (FIG. 2). Indeed, dendritic spine loss has been reported in the prefrontal cortex in post-mortem tissue from patients with bipolar disorders[53]. Cellular and molecular alterations that can alter neuronal interconnectivity are also under study in bipolar disorders, including mitochondrial dysfunction, endoplasmic reticulum stress, neuroinflammation, oxidation, apoptosis and epigenetic changes[54] (FIG. 2). However, as this line of research is still in its early stages, whether dysfunction of these pathways contributes to the development of bipolar disorder is not known. Other fields of research include those using induced pluripotent stem cells (iPSCs) derived from patients with bipolar disorders, which have been used to examine hyperexcitability in iPSC-derived neurons[55], or studies examining the possible role of the gut–brain axis[56,57]. Indeed, alterations in the gut microbiota composition or concentration might activate immunoinflammatory processes, changes in neuronal membrane permeability and oxidative stress[54]. Given that the core phenotype of the disorders is a biphasic energy shift, the corresponding monitoring of phasic dysregulation in mood, sleep and behaviour is attracting attention.

These neurobiological lines of research are aligned with the notion of the progressive course of bipolar disorders, which was first described by Kraepelin[58] and recently encompassed by the concept of neuroprogression[59]. The shortening of the interepisode interval after each episode recurrence and the reduced probability of treatment response with progression in a subset of patients putatively result from neurobiological interrelated processes in the brain[60]. Several hypotheses have been proposed to explain this concept of progression of bipolar disorders. For example, the kindling hypothesis speculates that alterations in brain plasticity lead to a gradual sensitization to stressors, which increases vulnerability to episode recurrence[61]. Moreover, the allostatic hypothesis proposes that repeated neurobiological stress, such as during an episode, requires biological adjustments that can increase allostatic load[62], increasing the risk of further episodes and precipitating and accelerating progressive illness. Neuroprogression encompasses the pathological 'rewiring' of the brain that occurs in parallel to the clinical and neurocognitive deterioration during the course of bipolar disorders. Several alterations, including increased neurodegeneration, neuronal apoptosis, neurotoxic susceptibility and altered neuroplasticity, which are driven by changes in inflammatory cytokines, corticosteroids, neurotrophins, mitochondrial energy generation, oxidative stress and neurogenesis, have been implicated in neuroprogression[59]. Neuroimaging changes in bipolar disorders are progressive and include grey matter loss in the left pars opercularis, left fusiform gyrus, left rostral middle frontal cortex and the hippcampus[63,64]. Staging models have been proposed according to the model of neuroprogression based on the number of relapses and functional impairment, although these are not currently used in clinical practice[65,66].

Diagnosis, screening and prevention

The classic and easily recognized bipolar disorder is bipolar I disorder, which is characterized by episodes of mania. Other bipolar disorders include bipolar II disorder and cyclothymia. The diagnosis of each disorder is based on different sets of behaviour and thought, which are divided somewhat arbitrarily on the degree of disruption in these areas. Additional characteristics include the development of psychotic symptoms.

In general, two sets of diagnostic criteria are used: the DSM-5 of the American Psychiatric Association and the ICD-10 of the WHO[4]. Updates to the ICD-10 (that is, the ICD-11) are expected in the near future; thus, the relative differences and utility of the ICD-11 and the DSM-5 remain to be determined. For the purposes of this Primer, we focus on the DSM-5.

Classification

Bipolar I disorder. As previously mentioned, bipolar I disorder is characterized by episodes of mania[67] (BOX 1). In the DSM-5, bipolar I disorder met twice the minimum criteria required to be recognized as a separate disorder, and diagnosis of bipolar I disorder was among the disorders with the highest inter-rater reliability in field trials[68,69].

Table 1 | **GWAS findings in bipolar disorder**

Gene[a]	Locus	Reproduced
PTGFR	1p31.1	No
LMAN2L	2q11.2	Yes
Several genes	3p21	Yes
TRANK1	3p22.2	Yes
ADCY2	5p15.31	No
MIR2113 and *POU3F2*	6q16.1	Yes
SYNE1	6q25.2	Yes
MAD1L1	7p22.3	No
ELAVL2	9p21.3	No
ADD3	10q25.1	No
ANK3	10q21.2	Yes
TENM4	11q14.1	Yes
CACNA1C	12p13.33	Yes
RHEBL1 and *DHH*	12q13.12	Yes
DGKH	13q14.11	No
ERBB2	17q12	No
NCAN	19p13.11	No
TRPC4AP	20q11.2	No

[a]The studied single-nucleotide polymorphisms are located within or near the gene. Modified from Budde et al.[34].
GWAS, genome-wide association study.

Box 1 | **Diagnosis of a manic or hypomanic episode according to the DSM-5**

Mania

- Mania is defined as a distinct period of abnormally and persistently elevated expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy. The period lasts ≥1 week and is present for most of the day, nearly every day (or for any duration of time if hospitalization is necessary). The mood disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. Additionally, the episode is not attributable to the physiological effects of a substance (for example, a drug of abuse, a medication or other treatment) or to another medical condition. During the manic period, at least three of the following symptoms (or at least four symptoms, if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behaviour:
- Inflated self-esteem or grandiosity
- Decreased need for sleep (for example, feeling rested after only 3 hours of sleep)
- More talkative than usual or feeling pressure to keep talking
- Flight of ideas or subjective experience that thoughts are 'racing'
- Distractibility (that is, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed
- Increase in goal-directed activity (either socially, at work, at school or sexually) or psychomotor agitation (that is, purposeless, non-goal-directed activity)
- Excessive involvement in activities that have high potential for painful consequences (for example, engaging in unrestrained buying sprees, sexual indiscretions or foolish business investments)

Hypomania

Hypomania is defined as above for mania although with a lower threshold for symptoms of lower severity; that is, symptoms do not cause occupational or social impairment. By definition, the symptoms are not severe enough to require hospitalization and are not psychotic in nature. The duration required to meet episode criteria is ≥4 days with an observable change by others from usual functioning. The presentation of psychotic symptoms during hypomania (although not depression) classifies the episode as manic.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[3].

The diagnosis of bipolar I disorder requires only a history of mania or the presence of mania (BOX 1); episodes of major depression are not required (BOX 2). In fact, ~5% of patients with bipolar I disorder have been estimated to experience only manic episodes (unipolar mania), although some of these patients might develop episodes of major depression later in life and can have subclinical depression. Hypomanic symptoms can occur in patients with bipolar I disorder (BOX 1) and might represent increasing instability for the patient and indicate that more intervention is needed to improve stability (for example, medication switching). Psychosis can also occur in individuals with bipolar I disorder and has been estimated to occur in up to 75% of patients with an acute manic episode[2]. In a long-term follow-up study of nearly 13 years, patients with bipolar I disorder were found to be symptomatically ill in 47.3% of follow-up weeks; patients had depressive symptoms during 31.9% of follow-up weeks and patients had manic or hypomanic symptoms for 8.9% of follow-up weeks[70]. Subsyndromal symptoms were three-times more frequent than syndromal episodes[70].

Bipolar II disorder. Bipolar II disorder is characterized by at least one hypomanic episode and one major depressive episode (BOXES 1,2). Symptoms must not be due to substance or medication use, or to other psychiatric or medical conditions. The course of illness is usually characterized by substantial and often prolonged periods of depression and periodic hypomanic symptoms. Perhaps because of this burden of depression, the overall degree of functional impairment and suicide risk is about the same for patients with bipolar II disorder as for those with bipolar I disorder[5]. The differential diagnosis of bipolar II disorder is often complicated by the dominance of depressive features. Several longitudinal studies have suggested that bipolar II disorder is a stable diagnosis that persists throughout the lifetime of an individual[71,72].

Psychotic symptoms can occur during bipolar II depressive episodes and have been reported in up to 50% of patients[2]. In a long-term follow-up study of 13 years, patients with bipolar II disorder were symptomatically ill in 53.9% of follow-up weeks. Patients had symptoms of depression in 50.3% of follow-up weeks and hypomania in 1.3% of follow-up weeks. Subsyndromal symptoms were three-times more frequent than major depressive symptoms[73].

Cyclothymia. Cyclothymia is a historically important diagnosis that describes everything from temperament to a prodrome of bipolar disorders. Cyclothymia is defined as mood instability for >2 years with both hypomanic and depressive symptoms that do not meet the criteria for hypomanic or depressive episodes. Some studies estimate that ≥30% of people diagnosed with cyclothymia develop a bipolar disorder, predominantly bipolar II disorder[74].

Other specified bipolar and unspecified bipolar and related disorders. These categories replace the 'not otherwise specified' category in the DSM-IV[75]. The other specified bipolar and related disorders are short-duration hypomanic episodes (2–3 days) and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, hypomanic episodes without prior major depressive episode, and short-duration cyclothymia (<2 years). Individuals with short-duration hypomanic episodes and major depressive episodes should be followed up. By contrast, the category 'unspecified bipolar and related disorders' is intended for temporary use, such as in emergency room settings in which insufficient evidence and information are available but the individual's behaviour and history suggest a diagnosis that falls into the bipolar and related disorders category[3].

Substance-induced and medication-induced bipolar and related disorders. This category includes symptoms of bipolar disorders such as mood instability and mania that are caused by any substance, medication or medical conditions. Examples include a cocaine-induced or amphetamine-induced manic episode or a medical condition (such as hyperthyroidism) causing manic symptoms. The difference between this group of diagnoses and the other categories is that when the causal element is removed, bipolar symptoms should not recur.

Specifiers. Specifiers are used to provide additional detail about the nature of the symptoms of an episode or throughout the course of the disorder (BOX 3). New additions to the DSM-5 bipolar and related disorders category include the specifiers 'with anxious distress' and 'with mixed features'. Other specifiers were continued from the DSM-IV to DSM-5, such as 'with rapid cycling', 'with melancholic features' or 'with atypical features' during depressive episodes and 'with psychotic features'. Other specifiers include 'with peripartum onset' and 'with seasonal pattern', which can be used for depressive and hypomanic or manic symptoms. Specifiers to be considered for inclusion in future updates to the DSM include predominant polarity (that is, either manic or depressive polarity), the presence of cognitive impairment, family history of bipolar disorders and age at onset (for example, using 18 years of age as a cut-off to define early onset).

The 'with mixed features' specifier can, for the first time, be used for symptoms of major depressive disorder or bipolar disorders. This specifier refers to the possibility that individuals in a manic episode can simultaneously experience symptoms of depression or, conversely, that patients can experience hypomanic symptoms during a depressive episode (BOX 3). The possibility of mixed symptoms is important for diagnosis and management for a number of reasons, not least of which is because mixed symptoms are associated with a more torpid course of disease and a higher likelihood of suicide[2]. However, this specifier, which replaced the DSM-IV 'mixed episode category' that required the simultaneous occurrence of a full manic and a full depressive episode, has not been without controversy[76]. Indeed, although European and North American literature recognizes that mixed symptoms can occur across the range of mood symptoms experienced by patients with bipolar disorders, a debate on how to define mixed features remains[77].

Box 2 | **Diagnosis of a major depressive episode according to the DSM-5**

A major depressive episode, by definition, affects a number of different arenas of human behaviour and thought. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning, and the episode is not attributable to the physiological effects of a substance or another medical condition. During a major depressive episode, at least one of the symptoms is either depressed mood or loss of interest or pleasure, and at least five of the following symptoms are present during the same 2-week period and represent a change from previous functioning:

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (for example, feels sad, empty or hopeless) or observation made by others (for example, appears tearful); in children and adolescents, mood can be irritable
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
- Significant weight loss when not dieting, weight gain (for example, a change of >5% of body weight in 1 month) or decrease or increase in appetite nearly every day; in children, failure to make expected weight gain can be considered
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (and not merely self-reproach or guilt about being sick)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (as indicated by either subjective account or observation)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[3].

Diagnostic work-up

Possibly one of the most important factors in the diagnosis of bipolar disorders is that individuals are typically very conscious of and sensitive to their depressive symptoms but do not recognize their hypomanic or manic symptoms. One question to ask patients is whether they have periods of depressive symptoms in which they have excessive energy or periods of extreme irritability and high activity, as this question can help the patient recognize symptoms other than depression. Indeed, the identification of past or current hypomanic or manic symptoms in patients who present with depression is critically important. Asking individuals about changes in activity and energy levels, not just mood, is also important, as changes in energy and activity levels might be more of a signifier of bipolar disorders than changes in mood[78,79]. Along this line, increasing activity or energy is actually required for bipolar mania diagnoses in DSM-5. In addition to asking patients about a history of depression and other types of episodes, including family members or partners in the evaluation is crucial, given that the patient might be unable to effectively observe or identify changes in their own behaviour, energy or mood. Owing to the high lifetime potential for suicide in patients with bipolar disorders, screening patients for suicide intent or plan is very important[24].

Several screening instruments that may be of possible benefit include life charting[80] (which can be used for mania, hypomania and depression), the Young Mania Rating Scale[81] and the Hypomania/Mania Symptom Checklist (HCL-32)[82,83]. Screening tools for bipolar disorders such as the Mood Disorders Questionnaire and HCL-32 are often used but have low sensitivity and specificity, especially in the community setting[84]. Major depressive episodes are similar in bipolar disorders and major depressive disorder, although mixed features are more common in patients with bipolar disorders than in those with major depression[85]. Several self-report questionnaires for the evaluation of depression are available, including the Patient Health Questionnaire-9 (PHQ-9) or the Inventory of Depressive Symptomatology (IDS)[86]. In addition, clinician-driven forms are available, including the Hamilton Rating Scale for Depression and the clinician version of the IDS[87]. As previously discussed, patients tend to be more aware of depressive symptoms than manic symptoms; thus, the use of self-report and clinician-driven forms for mania and hypomania is key to assess these symptoms.

Prevention

Some studies have suggested that early interventions in high-risk children and adolescents alter the course and

development of bipolar disorders[88]. These early interventions represent an emerging field, and those individuals at highest risk, such as children or adolescents with subsyndromal manic symptoms or children of patients with bipolar disorders, are providing important new information. The possible role of environmental factors (such as diet, physical activity and smoking, as well as stress, substance abuse or neurological insult) in the development of bipolar disorders is increasingly appreciated[43]. However, this work is still very early on in its development. Some groups are trying to identify the earliest biological symptoms of bipolar disorders and interventions that could change the course of illness.

Management

Bipolar disorders are highly recurrent, even when correctly diagnosed and treated. The effective treatment of acute depressive and hypomanic or manic symptoms and the prevention of relapses are essential according to several international guidelines, including the Canadian Network for Mood and Anxiety Treatments, the International College of Neuropsychopharmacology and the British Association for Psychopharmacology[89–91]. Accordingly, management of patients with bipolar disorders involves the acute treatment of manic or hypomanic episodes in addition to maintenance therapy to prevent relapses and further episodes.

Box 3 | **Specifiers for bipolar and related disorders in the DSM-5**

For mood episodes with mixed features

For clarity, the mood disorder committee of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) elected to exclude overlapping symptoms that could occur at either pole of mania or depression, which include irritability, distractibility or agitation[172]. Instead, the 'mixed features' specifier is defined by symptoms that occur only during hypomanic, manic or depressive episodes. Importantly, the specifier symptoms do not necessarily present throughout the day but could occur intermixed with symptoms required to meet episode criteria. However, these mixed symptoms occur only in the context of an episode because, when they occur separate from an episode, the diagnosis would change.

For a hypomanic or manic episode with mixed features, three of the following must be present during most days during the episode:

- Sad or depressed feeling
- Decreased interest or pleasure
- Psychomotor slowing
- Decreased energy or marked fatigue
- Feelings of extreme guilt or worthlessness
- Recurrent thoughts of suicide plan or even attempt

During a depressed episode with mixed features, three of the following need to be present during most days:

- Expansive or euphoric mood
- Increased grandiosity or self-esteem
- Pressured speech or pressure to keep talking
- 'Racing' thoughts or flight of ideas
- Increased goal-directed activity or agitation
- Excessive involvement in activities with possibly painful consequences
- Decreased need for sleep

For mood episodes with anxious distress

The presence of at least two of the following symptoms during most days during the episode:

- Feeling keyed up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful may happen
- Feeling that the individual might lose control of himself or herself

For mood episodes with psychotic features

- Delusions or hallucinations present at any time
- Psychotic features can be mood-congruent or mood-incongruent

For mood episodes with catatonia

The presence of at least three of the following symptoms:

- Stupor
- Catalepsy
- Waxy flexibility
- Mutism
- Negativism
- Posturing
- Mannerism
- Stereotypy
- Agitation
- Grimacing
- Echolalia
- Echopraxia

For mood episodes with peripartum onset

This specifier describes when the onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

For major depressive episodes with melancholic features

This specifier describes the loss of pleasure or lack of reactivity to usually pleasurable stimuli and occurs in the presence of at least three of the following symptoms:

- Profound despondency, despair and/or moroseness or empty mood
- Depression that is regularly worse in the morning
- Early morning awakening
- Marked psychomotor agitation or retardation
- Significant anorexia or weight loss
- Excessive or inappropriate guilt

For major depressive episodes with atypical features

- Mood reactivity
- The presence of at least two of the following symptoms:
  - Significant weight gain or increase in appetite
  - Hypersomnia
  - Leaden paralysis
  - A long-standing pattern of interpersonal rejection sensitivity

Course specifier 'with rapid cycling'

- Can be applied to bipolar I or bipolar II disorder
- Describes the presence of at least four mood episodes in the previous 12 months

Course specifier 'with seasonal pattern'

- Regular seasonal pattern of at least one type of episode

Table 2 | **Agents approved by the US FDA for acute bipolar mania, bipolar depression and maintenance**

Drug	Mania or mixed features	Depression	Maintenance	Comments	Adverse effects
Mood stabilizers					
Lithium	Yes[a]	No	Yes	Has anti-suicidal properties	Reduced renal function
Carbamazepine (extended-release)	Yes	No	No	Useful for treatment of patients with non-classic features	CYP450 inducer
Divalproex (delayed release)	Yes	No	No	Useful for treatment of mixed states	CYP450 inhibitor; teratogenic (for example, can cause spina bifida)
Divalproex (extended release)	Yes	No	No		
Lamotrigine	No	No	Yes	Depressive predominant polarity; requires slow titration	Steven Johnson syndrome
Antipsychotics					
Aripiprazole	Yes[a]	No	Yes	Manic predominant polarity; good metabolic profile	Akathisia (restlessness and an inability to remain still)
Asenapine	Yes	No	No	Possibly effective for depressive symptoms	Moderate metabolic syndrome
Cariprazine	Yes	No[b]	No	Good metabolic profile	Akathisia
Chlorpromazine	Yes	No	No	Has a rapid efficacy	Risk of switch to depression; extrapyramidal symptoms
Lurasidone	No	Yes[c]	No	Lack of anticholinergic effects; efficacy related to feeding	Akathisia and sedation
Olanzapine	Yes[a,c]	No	Yes	Rapid efficacy	Severe metabolic syndrome
Olanzapine–fluoxetine	No	Yes	No		
Quetiapine (immediate-release)	Yes[a,c]	Yes[d]	Yes[e]	Antipsychotic with indications for treatment of acute manic and depressive episodes and maintenance	Sedation
Quetiapine (extended release)	Yes	Yes[d]	No		
Risperidone	Yes[a,c]	No	No	Intramuscular administration monthly	Risk of switch to depression; extrapyramidal symptoms
Ziprasidone	Yes	No	Yes[e]	Manic predominant polarity; good metabolic profile; efficacy is related to feeding	Hypotension

CYP450, cytochrome p450. [a]Approved for children or adolescents. [b]Cariprazine was superior to placebo in reducing depressive symptoms in patients with bipolar I disorder in randomized, double-blind, placebo-controlled studies. [c]Also approved for adjunctive therapy to lithium or valproate. [d]Including patients with bipolar II disorder. [e]Approved for combination therapy with lithium or valproate.

Lithium was the first medication approved by the US FDA for the treatment of acute mania and since then, for adults, ten medications have been approved by the FDA for the treatment of acute mania, three for the treatment of bipolar depression and six for maintenance therapy (TABLE 2). For children and adolescents, five medications are approved for acute mania by the FDA (TABLE 2). The approvals of most of these therapies were based on results from randomized, double-blind, placebo-controlled studies using DSM-IV diagnostic criteria, although some medications have also been used or studied for treatment without FDA approval. However, importantly, results from pivotal clinical trials are not necessarily generalizable to the real-world population because most patients with comorbidities, especially those with substance use disorders, were excluded from these trials[92]. Indeed, one example of this limitation is the lack of superiority of quetiapine (extended-release) compared with placebo in reducing depressive symptoms in patients with multiple comorbidities[93]. Comorbidities in bipolar disorders are frequent, and appropriate treatments for these conditions represent an urgent unmet need.

Despite available therapies for bipolar disorders, treatment loses effectiveness when adherence is uncertain. Thus, enhancing adherence is one of the cornerstones in the management of patients with bipolar disorders. In addition, balancing short-term and long-term effectiveness and safety for all drugs in patients with bipolar disorders is essential[94].

Treatment of acute mania

Pharmacological therapy is the cornerstone treatment for acute mania (TABLE 2), although nonpharmacological treatments can be used in patients with treatment-resistant and severe mania. The treatment for hypomania has scarcely been addressed, and pharmacological approaches for mania have been assumed. Differences in the reported efficacy of the FDA-approved therapies for the treatment of mania in adults are small, especially on the basis of data from head-to-head comparison studies, although some multiple-treatment network meta-analyses have suggested a stronger efficacy of some therapies[95,96]. By contrast, the adverse-effect profiles of therapies for mania is widely variable[97] (TABLE 2).

A more-recent meta-analysis supports that when a patient does not respond after 1–2 weeks, a different medication should be considered[98]. The combination of a mood stabilizer and an antipsychotic, especially for more-severe illness, may be a better choice than either medication alone[99]. In children and adolescents, the antipsychotic risperidone had a higher efficacy than lithium and divalproex sodium but was associated with more-severe metabolic adverse effects[100].

Despite several antipsychotics showing superiority to placebo at reducing manic symptoms (such as haloperidol and paliperidone monotherapy), none has been approved for this indication[95]. Several other investigated therapies, such as lamotrigine, eslicarbazepine and topiramate monotherapy or combined gabapentin and mood stabilizer, were not superior to placebo[95]. Other drug classes, including NSAIDs (celecoxib), dopamine agonists (bromocriptine), protein kinase C inhibitors (tamoxifen) and xanthine oxidase inhibitors (allopurinol), have also been studied in acute mania as monotherapy or adjunctive therapy[99]. The sample sizes of those studies were small, and the results were generally inconclusive.

ECT as a monotherapy or an adjunctive therapy to pharmacological treatments can also be used for the treatment of acute mania, especially in patients with refractory mania or those with aggressive behaviour and/or psychosis[101]. Two studies showed the efficacy of repetitive transcranial magnetic stimulation of the right prefrontal cortex for the treatment of acute mania in adults, although one study in adolescents was ineffective[102,103]. In addition, dysfunction of the circadian system is thought to be a main factor for the onset of mania and, accordingly, one study showed an effect of blue light-blocking glasses (when used as an additive to standard pharmacological treatment) in reducing manic symptoms compared with standard treatment alone[104]. Cognitive–behavioural therapy (CBT) was suggested to improve the severity of manic symptoms in one meta-analysis[105].

Treatments for acute depression

Although patients with bipolar disorders spend more time in depression than in mania or hypomania, fewer studies focus on depression, and only three medications — all antipsychotics — have been approved by the FDA for bipolar depression. Patients with depression are more sensitive to, but less tolerant of, pharmacological treatments — especially antipsychotics — than they are during mania[106]. Accordingly, a lower starting dose and slower titration might be necessary for patients with depression. In addition, antipsychotic-induced metabolic abnormalities have become a major concern, and monitoring weight changes and metabolic profiles at each health-care visit should be routine. Notably, short-term weight gain cannot accurately predict long-term weight gain[97] and self-reported weight change is unreliable[107].

Given the limited number of approved medications for bipolar depression, off-label use of therapies, or combinatorial therapy, is common. In this context, some treatments, including anticonvulsants (such as divalproex and lamotrigine), olanzapine monotherapy and combined lithium and lamotrigine therapy, were superior to placebo in reducing the severity of depressive symptoms in patients with bipolar disorders[108]. In addition, quetiapine–lamotrigine combination therapy was superior to quetiapine alone[109]. Lurasidone, which is approved by the FDA for the treatment of bipolar depression in adults, has shown compelling results in acute depression in trials in children and adolescents with bipolar disorders[110].

Little evidence supports the possible benefits of anticonvulsants (such as levetiracetam, topiramate and gabapentin), thyroid hormone, acetylcholinesterase inhibitors, acetyl-L-carnitine, pregnenolone, naltrexone or lisdexamfetamine, either as adjunctive therapy or monotherapy, for bipolar depression. However, studies with a small sample size have shown efficacy of pramipexole, ketamine and scopolamine for bipolar depression. Anti-inflammatory agents such as NSAIDs, *N*-acetylcysteine, omega-3 polyunsaturated fatty acids and pioglitazone might also have antidepressant effects in bipolar depression when used adjunctive to conventional therapy[111].

The controversy surrounding the efficacy of antidepressants in acute bipolar depression and the risk of mood switching to hypomanic episodes, manic episodes or mixed states, particularly with monotherapy, remains unsettled[46]. One meta-analysis of 15 trials including a total of 2,373 patients showed that antidepressants were not superior to placebo treatment[112], although another meta-analysis that focused on adjunctive second-generation antidepressants reported only positive effects[113,114]. However, agomelatine treatment was not superior to placebo in patients with bipolar depression[115]. In addition, an increased risk of switching to mania or hypomania and cycle acceleration has been reported with stimulant-like agents and pramipexole. A traditional mood stabilizer should be started first, before antidepressants or other drugs that can induce switching to mania, and manic or hypomanic switching should be monitored closely when using mania-provoking agents.

Nonpharmacological treatments for bipolar depression include ECT, repetitive transcranial magnetic stimulation, deep brain stimulation, vagus nerve stimulation, lifestyle interventions and psychotherapies. ECT is commonly used for treatment-refractory depression and is effective for the treatment of both bipolar depression and unipolar depression[116]. Indeed, ECT had a significantly higher responder rate than algorithm-based pharmacological treatments in patients with treatment-resistant bipolar depression[117]. Psychotherapy, such as psychoeducation, CBT, family-focused therapy, dialectical behaviour therapy, mindfulness-based CBT and interpersonal and social rhythm therapy, might be useful primarily as adjunctive treatments for managing bipolar depression[118]. However, the usefulness of each intervention has been studied only in specific patients with specific symptoms of bipolar disorders[105,119]. In children and adolescents, family psychoeducation, in addition to skill building and CBT, might be effective for bipolar depression[120].

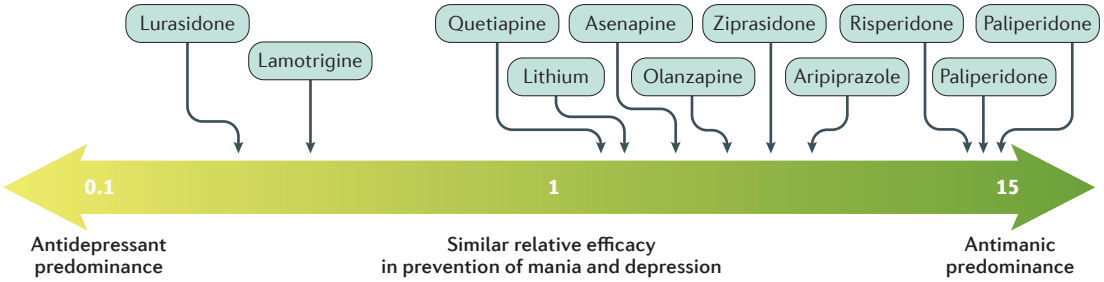

Figure 3 | **Polarity index.** The polarity index of drugs used for the maintenance treatment of patients with bipolar disorders is the ratio of the number of patients needed to treat for prevention of depression to the number of patients needed to treat for prevention of mania on the basis of results of randomized placebo-controlled trials[173]. This index classifies therapies as those with an antimanic prophylactic effect and those with an antidepressant prophylactic effect. A polarity index of 1 reflects an equal efficacy in preventing manic and depressive episodes.

Maintenance treatment

Considering the recurrent and chronic nature of bipolar disorders, optimal long-term management requires a preventive strategy that includes pharmacological treatments, psychological therapies and lifestyle approaches[121] shortly after onset[122]. Pharmacotherapy (most commonly a mood stabilizer alone or in combination with an antipsychotic or an antidepressant[123]) in addition to tailored psychosocial interventions can decrease the risk of relapse, improve treatment adherence and reduce the number and length of hospitalizations[90].

Lithium remains one of the most effective drugs for the prevention of both manic and depressive episodes, and one network meta-analysis reported a risk ratio of 0.62 (95% credible interval 0.53–0.72) for the risk of mood relapse or recurrence compared with placebo[124]. In addition, lithium monotherapy and combined lithium–valproate therapy were found to be more likely to prevent relapses in patients with bipolar I disorder than valproate monotherapy, regardless of the severity of illness in the BALANCE study[125]. However, adjunctive lithium to optimized personalized treatment had no additional benefit compared with optimized personalized treatment alone[126]. Nevertheless, the lithium plus optimized personalized treatment group had less exposure to second-generation antipsychotics and the subsequent adverse effects[126]. Despite the effectiveness of lithium, this drug has been associated with a decline in renal function and the development of hypothyroidism and hypercalcaemia following long-term use[124,127]. Quetiapine and combined quetiapine–lithium and quetiapine–divalproex therapy have also been suggested as suitable therapies for the maintenance treatment of patients with bipolar disorders on the basis of data from meta-analyses[124,128]. Indeed, no clinically meaningful differences were found between lithium treatment or treatment with quetiapine and adjunctive personalized treatment in the CHOICE study[129]. Nevertheless, these data should be interpreted with caution, as treatments were initiated during an acute episode in most trials (mostly during an acute manic episode) and the polarity of the episode affects the potential of the treatment to prevent further episodes of the similar polarity[130]. Furthermore, many industry-led trials were enriched designs, which may inflate the efficacy of the studied drug[91]. Evidence for pharmacological maintenance therapies in children and adolescents is practically limited to the acute treatment of manic and mixed episodes[108].

Pharmacological maintenance treatment should be aligned with the patient's predominant polarity, which is defined as the pole at which a patient has at least twice as many episodes as at the other pole. However, polarity is not observed in all patients. Predominant polarity has prognostic value and clinical and therapeutic implications[131]. The polarity index is a metric used to classify maintenance therapies and categorizes therapies as those with a predominant antimanic prophylactic profile and those with an antidepressant prophylactic profile (FIG. 3). For example, patients with a depressive predominant polarity (mostly those with bipolar II disorder) might have a better response to lamotrigine and are more likely to require adjunctive antidepressants. Conversely, patients with a manic predominant polarity (mostly those with bipolar I disorder) have a better response to atypical antipsychotics such as risperidone[92,132,133]. Quetiapine and lithium have a polarity index nearest to 1, reflecting a near-equal efficacy in preventing manic and depressive episodes.

For nonpharmacological treatment, psychoeducation has shown long-lasting prophylactic effects in individuals with bipolar disorders who attended group psychoeducation for 6 months[134]. Indeed, at 5-year follow-up, patients who received psychoeducation had a longer time to recurrence, had fewer recurrences, spent less time in an episode and had reduced duration of hospitalization[135]. CBT[136], interpersonal and social rhythm therapy[137] and family-focused therapy[138] have also reported efficacy for bipolar maintenance therapy. Recently, functional remediation (a restoring psychosocial therapy that uses ecological neurocognitive techniques) has improved functioning in patients with bipolar I disorder[139] and patients with bipolar II disorder[140] with psychosocial functional impairment. Moreover, improvement in psychosocial functioning has been shown to remain after 1-year follow-up[141]. Internet-based approaches and applications are gaining traction and are starting to be used in clinics[13,142]. In general, CBT, family-focused therapy

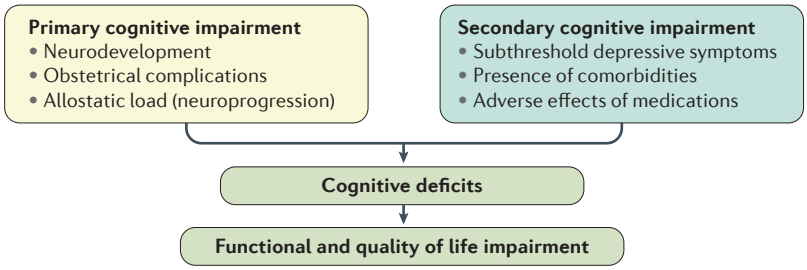

Figure 4 | **Sources of cognitive dysfunction.** Cognitive impairment is common in patients with bipolar disorders and can be primary or secondary in origin. Either way, cognitive impairment strongly affects functional and quality of life impairment in patients.

and psychoeducation have a more antidepressant than antimanic prophylactic effect, whereas caregiver group psychoeducation has a more antimanic effect[143].

Valproate and carbamazepine are not recommended for the treatment of women of childbearing age as they increase the risks of spina bifida and low IQ in offspring[89]. In this subpopulation, preconception counselling and planning are crucial to avoid the teratogenic effects of drugs, in particular during the first trimester, and the abrupt cessation of a treatment, which imply an undeniable risk of recurrences of a mood episode in the mother.

Quality of life

Bipolar disorders are associated with reduced quality of life that can be more severe than that which occurs in other mood or anxiety disorders[144]. Poor quality of life correlates with depressive symptoms more than manic or hypomanic symptoms[144]. In addition, poor quality of life is associated with residual depressive symptoms that can occur during remission[145] and the high comorbidity of bipolar disorders with anxiety disorders[146]. Quality of life also comprises individuals' perceptions of their position in life in the context of their culture, value system, personal goals, expectations and standards[147]. Thus, quality of life depends not only on clinical remission but also on functional recovery[148]. Accordingly, poor quality of life is closely associated with socio-occupational disability, including reduced academic attainment and workforce capacity[149] and difficulties with activities of daily living[150], employment status and personal relationships. Indeed, the unemployment rate is 4–10-times higher[151] and the divorce and separation rate is 2–3-times higher in patients with bipolar disorders than in the general population[152]. The frequent onset of bipolar disorders around 20 years of age interferes with age-appropriate educational, social and developmental tasks as well as the development of a sense of self and identity[153]. Thus, the fairly early onset is a key reason for academic underattainment and poor vocational integration[108].

Other contributors to poor occupational outcomes in patients with bipolar disorders include the presence of persistent cognitive impairment, including impairments in memory and executive function — notwithstanding that people with the highest premorbid intellectual functioning are at greatest risk of developing the disorder[154] (FIG. 4). Substantial cognitive impairment has been reported in 50–70% of patients during periods of remission[155,156]. Patients with cognitive impairment have poorer quality of life, increased stress and lower work capacity than patients who are cognitively intact, despite comparable levels of subsyndromal mood symptoms[155,156]. Indeed, meta-analyses have indicated that impairments in memory and executive function are stronger contributors to poor occupational outcome than residual mood symptoms[157].

Functional remediation is a recently developed psychological intervention that aims to restore psychosocial functioning in patients with several disorders and has shown beneficial effects on functional capacity that persist for ≥1 year after treatment completion in patients with bipolar disorders[139,141]. No clinically available treatments for cognitive dysfunction in patients with bipolar disorders are currently available, although preliminary evidence points to potential superiority of lithium compared with alternatives[158]. Several candidate treatments, including erythropoietin, mifepristone, *N*-acetylcysteine[159], cognitive remediation therapy[160] and lurasidone, have been studied and have shown beneficial effects, mostly for the treatment of cognitive impairment[161]. Treatments targeting cognitive and functional impairments could increase quality of life in patients with bipolar disorders by enhancing academic attainment, work capacity and social relations and are a major strategic focus for the next decade.

Outlook

Over the past 30 years, the traditional concept of 'bipolar disorder' has evolved into a range of interconnected conditions that vary in terms of severity, frequency and polarity of mood shifts. Severe affective psychoses and milder syndromes, such as cyclothymia, are now recognized under the umbrella term of bipolarity and might share some common aspects of their pathophysiology and response to treatments[108]. In addition, the general adolescence onset (and, in rare cases, before puberty) is now recognized, although there is an ongoing controversy regarding the underdiagnosis versus overdiagnosis of bipolar disorders in children in certain countries[162].

Study design and experimental techniques

Regarding the genetics and pathogenesis of bipolar disorders, we need to widen our horizon and use new techniques and strategies. Diagnostic criteria should still be studied, focusing on the biology underlying the course, outcome and recovery of these disorders. Sample sizes of pharmacogenetics studies should be increased, and genomic approaches should be complemented using other techniques, such as epigenomics, proteomics, transcriptomics and metabolomics. In addition, research should include populations from around the world to develop a global overview of the genetic and environmental liability factors for bipolar disorders. The analysis of big actimetric (that is, data from non-invasive monitoring of human rest or activity cycles) and biomarker data using machine learning techniques may enable a probabilistic approach from a multifactorial perspective involving more variables than can be

managed by a clinician alone. Psychiatry will be increasingly computerized, which might be particularly helpful for bipolar disorders, as the disease courses can be seemingly chaotic and unpredictable to the human eye. Above all, these endeavours must adhere to the idea of data sharing, fostering collaboration between clinicians and basic scientists that should offer hope to and potentially cure millions of patients.

Staging and stage-specific treatments

Awareness of the importance of staging bipolar disorders is increasing, which will establish more tailored pharmacological and psychological treatments. Interest in early intervention is also increasing. Early intervention needs to be minimally invasive and almost free of adverse effects, given the nonspecific prodromal symptoms and the high risk of false positives[163]. After confirmed diagnosis, speaking openly about disease with patients and their families is important, as is implementing long-term treatment strategies and psychoeducation. For patients in late stages of these disorders, interventions used for treatment-refractory patients might be the most effective[117,164,165].

New therapies and personalized treatment

Improvements in our understanding of the pathophysiology of bipolar disorders are expected and should lead to more accurate diagnosis and improved treatments. The traditional randomized placebo-controlled trial paradigm needs to be challenged if we are to progress towards precision psychiatry[166,167]. This progress requires improving our ability to define a condition through molecular psychopathology[168] and specific biomarkers; currently, most available biomarkers are approximate correlates of systemic stress or chronic brain damage[54]. The stratification of patients using other specifiers (such as predominant polarity or early onset), which are absent in the DSM-5 (REF. 169), might also help to design tailored treatment regimens. Over the coming decades, more attention will be given to the complications of bipolar illness, including comorbidities (diabetes mellitus, osteoporosis, metabolic syndrome and hypertension), suicide and cognitive impairment. New treatments based on chemical, physical and psychological paradigms may be designed to tackle specific dimensions of the disease. 'Big' and 'thick' 'data will be equally important for that endeavour.

Large observational studies and large, good-quality patient registries might be particularly important to increase the external validity of the data gathered from controlled studies, as treatment guidelines are based on trials that are conducted in cohorts that represent <5% of the true population with bipolar disorders (such as patients with no comorbidities, those with no risk of suicide, those using contraceptive measures and those who are willing to participate in trials, among others)[90,91]. Of the drugs in the current pipeline, 50% are derived from currently available therapies that are based on traditional targets, such as dopamine and serotonin receptor antagonists or inhibition of monoamine transport, among others[89]. Long-acting formulations of currently available drugs are currently underused in bipolar I disorder with manic predominant polarity. However, some innovative approaches are ongoing, such as drugs acting through glutamatergic pathways, such as ketamine, esketamine and rapastinel, some of which are in later-stage clinical trials, for the treatment of bipolar depression. These drugs might provide rapid relief to bipolar depression and suicidality and could ultimately change our approach to the treatment of bipolar depression, although the risks of dependency, other adverse effects and long-term effectivness remain to be established[170]. Lastly, new brain stimulation techniques that could improve the treatment of difficult cases are also under study[171].

Finally, the prevention of bipolar disorders will become paramount, including primary prevention by promoting healthy physical and emotional habits, increasing cognitive reserve, stress management and new substance use policies. In parallel, improved understanding of the mechanisms underlying the regulation of emotions, maturation and brain function in healthy individuals will help to identify specific circuits and pathways as targets for novel therapeutic approaches.

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Acknowledgements

E.V. is grateful for the support received from the Instituto de Salud Carlos III, Ministry of Economy and Competitiveness of Spain (PI 12/00912), integrated into the Plan Nacional de I + D + I and co-funded by ISCIII-Subdirección General de Evaluación and Fondo Europeo de Desarrollo Regional (FEDER); Centro para la Investigación Biomédica en Red de Salud Mental (CIBERSAM), Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014_SGR 398), the Seventh European Framework Programme (ENBREC); and the Stanley Medical Research Institute. M.B. is supported by an Australian National Health and Medical Research Council Senior Principal Research Fellowship (GNT1059660) and has received grants from the US NIH, the Australian Cooperative Research Centre, the Simons Autism Foundation, the Cancer Council of Victoria, the Stanley Medical Research Foundation, the Medical Benefits Foundation, Beyond Blue, Rotary Health and the Geelong Medical Research Foundation. T.G.S. receives funding from Deutsche Forschungsgemeinschaft (DFG; SCHU 1603/5-1 and SCHU 1603/7-1), the German Federal Ministry of Education and Research (BMBF; 01ZX1314K, 01EE1404H and 01EE1404H), and the Dr Lisa Oehler Foundation (Germany). A.F.C. is supported by a research fellowship award from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; Brazil). T.S. has received grant funding from the Stanley Medical Research Institute and Palo Alto Health Sciences Services. J.R.C. has received federal funding from the US Department of Defense, the US Health Resources Services Administration and the US National Institute of Mental Health. K.G. has received grant support from the Brain and Behaviour Research Foundation and the Cleveland Foundation. K.W.M. is supported by the Lundbeck Foundation Fellowship (R21520154121). I.G. is supported by the Instituto de Salud Carlos III, Ministry of Economy and Competitiveness of Spain (Juan Rodés Contract (JR15/00012) and a grant (PI16/00187)), integrated into the Plan Nacional de I + D + I and co-funded by ISCIII-Subdirección General de Evaluación and FEDER.

Author contributions

Introduction (E.V.); Epidemiology (M.B.); Mechanisms/pathophysiology (T.G.S., A.F.C. and I.G.); Diagnosis, screening and prevention (T.S.); Management (J.R.C., K.G. and I.G.); Quality of life (K.W.M.); Outlook (E.V.); and Overview of Primer (E.V.).

Competing interests

E.V. has received grants and honoraria from AstraZeneca, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, H. Lundbeck, Janssen, Otsuka, Pfizer, Sanofi-Aventis, Sunovion and Takeda. M.B. has received research grants from Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, the Meat and Livestock Board, Mayne Pharma, Novartis, Organon, Servier and Woolworths. M.B. has also acted as a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, H. Lundbeck, Janssen-Cilag, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth and has served as a consultant to AstraZeneca, Bioadvantex Pharma, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, H. Lundbeck, Janssen-Cilag, Merck and Servier. T.S. has received grant funding from Elan Pharma International, Merck and Sunovion and has received personal fees from AstraZeneca, CMEology, Global Medication Education, H. Lundbeck, Medscape Education, Merck and Sunovion, and has received royalties from Jones & Bartlett Learning and UpToDate. J.R.C. has received grant support from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Cephalon (now Teva Pharmaceutical Industries), Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, H. Lundbeck, Intra-Cellular Therapies, Janssen, Pfizer,, Sunovion and Takeda. J.R.C. has also served as a consultant, advisory board member and speaker for Abbott Laboratories, Allergan, AstraZeneca, Bristol-Myers Squibb, Cephalon (now Teva Pharmaceutical Industries), Dainippon Sumitomo Pharma, GlaxoSmithKline, H. Lundbeck, Janssen, Merck & Co., Otsuka, Pfizer, Repligen, Servier, Solvay, Sunovion and Takeda. K.G. has been on a speakers' bureau and an advisory board of Sunovion and has received grant support from AstraZeneca. K.W.M. has received consultancy fees in the past 3 years from Allergan and H. Lundbeck. I.G. has consulted for Ferrer and has been a speaker for Ferrer and Janssen-Cilag. T.G.S. and A.F.C. declare no competing interests.

Publisher's note

Reviewer information

Nature Reviews Disease Primers thanks T. Kato, M. Leboyer, I. Melle, and the other anonymous reviewer(s), for their contribution to the peer review of this work.

How to cite this article

Vieta, E. et al. Bipolar disorders. *Nat. Rev. Dis. Primers* **4**, 18008 (2018).